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10/509,712	09/30/2004	Detlef P. Muller-Schulte	RO0909US(#90568)	2617

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,712	MULLER-SCHULTE, DETLEF P.	
	Examiner	Art Unit	
	Unsu Jung	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21-23 and 25-32* is/are pending in the application.

4a) Of the above claim(s) *8-13,29 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,14-19,21-23,25-28,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's reply filed on August 13, 2007 has been acknowledged and entered. The reply included amendments to the specification and claims 1-7, 14-19, and 28 and addition of new claims 29-32.

Election/Restrictions

2. Newly submitted claim 29 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 29 is directed to silica gel particles having functional groups being coupled to at least one biomolecule amino bearing group, said biomolecule amino bearing group being selected from the group consisting of proteins, peptides, nucleic acids, and oligonucleotides. The species of biomolecules are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1 as set forth in the Restriction Requirement dated October 16, 2006.

Since applicant has received an action on the merits for the originally presented species of biomolecule, streptavidin, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 29 has been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Regarding newly submitted claim 32, it is noted that claim 32 is directed to the "use" of spherical, luminescent silica gel particles. "Use" claims are non-statutory under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). See MPEP 2173.05(q).

Therefore, claim 32 have been withdrawn from consideration as being drawn to non-statutory subject matter. If these claims are amended to recite statutory subject matter, the amended claims may be rejoined with the appropriate invention Group as set forth in the Restriction Requirement set forth on October 16, 2006.

4. Claims 1-19, 21-23, and 25-32 are pending, claims 8-13, 29, and 32 have been withdrawn from consideration, and claims 1-7, 14-19, 21-23, 25-28, 30, and 31 are under consideration for their merits.

Oath/Declaration

5. A new declaration with acknowledgement of the filing of foreign application GE 102 14 019.7 has been received.

Information Disclosure Statement

6. It is acknowledged that the missing pages and publication information for the references cited in IDS's submitted on September 30, 2004 and April 11, 2005 as indicated in the previous Office Action dated April 10, 2007 (see items 4-6) are being obtained by the Applicant and will be provided to the Office as soon as such information is available.

Objections Withdrawn

7. Applicant's arguments, see pp14-15, filed on August 13, 2007, with respect to the objection of the specification have been fully considered and are persuasive. The objection of the specification has been withdrawn in view of amended claim 2 and specification in the reply filed on August 13, 2007.

Rejections Withdrawn

8. Applicant's arguments, see p15, filed on August 13, 2007, with respect to the rejection under 35 U.S.C. 112, second paragraph have been fully considered and are persuasive. The rejection of claim 2 under 35 U.S.C. 112, second paragraph has been withdrawn in view of amended claim 2 in the reply filed on August 13, 2007.

9. Upon further consideration, the rejection of claims 3-6 and 25 under 35 U.S.C. 102(b) as being anticipated by Walt et al. (U.S. PG Pub. No. US 2001/0029049 A1, Oct. 11, 2001) has been withdrawn. With respect to claims 3-6 and 25, Walt et al.

does not teach the luminescent silica gel particles, wherein the luminescent substance is luminescent protein. Similarly, the rejection of claim 7 under 35 U.S.C. 102(b) as being anticipated by Walt et al. (U.S. PG Pub. No. US 2001/0029049 A1, Oct. 11, 2001) in light of Schwarzberg (U.S. Patent No. 4,235,869, Nov. 25, 1980) has been withdrawn since Walt et al. does not teach the luminescent silica gel particles, wherein the luminescent substance is luminescent protein.

10. Upon further consideration, the rejection of claim 28 under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. PG Pub. No. US 2001/0029049 A1, Oct. 11, 2001) in view of Müeller-Schulte (WO 02/09125 A1, Jan. 31, 2002) as applied to claim 15 above, and further in view of Tom-Moy et al. (U.S. Patent No. 5,527,711, June 18, 1996) in favor of the new rejection of claim 28 under 35 U.S.C. 103(a) as being unpatentable over Walt et al. in view of Müeller-Schulte, and further in view of Kleiber et al. and Tom-Moy et al. as set forth in item 23 below because Kleiber et al. teaches that the aldehyde groups of Walt et al. in view of Müeller-Schulte covalently couple with streptavidin.

Claim Objections

11. Claims 15 and 25 are objected to because of the following informalities: the term "luminescent polymer particles" in line 1 of claim 15 should be corrected to "luminescent silica particles" in order to be consistent with the particle term recited in claim 1 since

the term "luminescent polymer particles" of claim 15 is referring to the particles of claim 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 15-18, 28, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 15 and all dependent claims thereof, the phrase "further comprising a magnetic colloid" in lines 2-5 is vague and indefinite. It is unclear whether or not the term "a magnetic colloid" of claim 15 is referring to "a magnetic colloid" in line 10 of claim 1. For the purpose of examination, the term "a magnetic colloid" of claim 15 has been interpreted as being the same as the term "a magnetic colloid" of claim 1 as the specification teaches that silica particles comprise encapsulated magnetic colloids and does not teach any additional magnetic colloids further comprising the silica particles (p10, paragraph [000058]-p11, paragraph [000060])

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Walt et al. (U.S. PG Pub. No. US 2001/0029049 A1, Oct. 11, 2001).

Walt et al. anticipates instant claims by teaching a spherical luminescent silica gel particles (see entire document) containing a transparent silica gel matrix (p7, paragraph [0077]), said transparent silica gel matrix having at least one luminescent substance (p9, paragraph [0085]), the size of said particle being at least 0.5 μm (p9, paragraph [0089]).

With respect to claim 2, Walt et al. teaches luminescent silica gel particles, which includes fluorescein (p8, paragraph [0081]) that would not be autofluorescent.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

18. Claims 3-6, 14, 25, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. PG Pub. No. US 2001/0029049 A1, Oct. 11, 2001) in view of Chen et al. (*Chem. Mater.*, 1995, Vol. 7, pp1779-1783).

Walt et al. teaches luminescent silica gel particles (see item 15 above). Walt et al. further teaches a sensor array comprising a luminescent silica gel particles and that variety of fluorescent dyes can be employed to optically encode silica gel particles (p8, paragraphs [0081] and [0082]).

With respect to claim 6, Walt et al. teaches that any two of the luminescent substance display different emission frequencies (p8, paragraph [0082]).

With respect to claim 25, Walt et al. teaches a sensor array comprising a luminescent silica gel particles (Abstract) containing a transparent silica gel matrix (p7, paragraph [0077]), said transparent silica gel matrix having at least one luminescent substance (p9, paragraph [0085]). With respect to the limitation of "for at least one of

the analysis or diagnostic testing of nucleic acids, nucleic acid fragments, proteins, peptides, antibodies, antibody fragments, cells, cell receptors, and biotinylated biomolecules and testing protein or nucleic acid libraries," a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The sensor array of Walt et al. meets all the structural limitations of claim 25 and would therefore be capable of performing the intended use of "analysis or diagnostic testing of nucleic acids, nucleic acid fragments, proteins, peptides, antibodies, antibody fragments, cells, cell receptors, and biotinylated biomolecules and testing protein or nucleic acid libraries."

However, Walt.et al. fails to teach luminescent silica gel particles, wherein the luminescent substance is a luminescent protein.

Chen et al. teaches a method of making optically transparent biomaterial using sol-gel encapsulation method, in which fluorescent proteins such as phycobiliproteins are added to a silica sol (see entire document, particularly p1780, *Methods*).

With respect to claims 3 and 14, Chen et al. teaches that the luminescent protein is encapsulated in silica particles (p9, paragraph [0085]).

With respect to claim 4, Chen et al. teaches the luminescent substance displays fluorescence (p1780, Methods).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ the sol-gel encapsulation method of Chen et al, in which

fluorescent proteins such as phycobiliproteins are added to a silica sol, in order to produce optically encode silica particles of Walt et al. The advantage of optically encoding silica particles, which exhibit characteristic, i.e. unique, optical signature to a reference analyte, provides the motivation to combine teachings of Walt et al. and Chen et al. with a reasonable expectation of success as optically encoded silica particles (luminescent silica particles) with unique, optical signature can be conveniently decoded for identification of reference analyte for use in biochemical assays. Further, it would have been obvious to one of ordinary skill in the art at the time of the invention to select a fluorescent (luminescent) protein as a fluorescent dye, since it has been held to be within the general skill of a worker in the art to select a known material on the basis of its suitability for the intended use as a matter of design choice. *In re Leshin*, 125 USPQ 416. Because the claimed particle is known in the prior art and has been disclosed as being capable of being labeled with fluorescent dyes in general, the selection of a specific type of fluorescent dyes in itself does not present a novel feature of the claimed invention. Since one of ordinary skill in the art at the time of the invention would recognize that the particle of Walt et al. could be labeled with variety of different types of fluorescent dyes known in the optical arts, it would have been obvious to employ fluorescent proteins as the fluorescent dyes in the instant claim.

With respect to claim 5, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value for a result effective variable. Section 2144.05 [R3] of the MPEP presents case law upholding obviousness rejections based on optimization of ranges:

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.)

The specification does not disclose that the specifically claimed range(s) of "1 to 10%-wt concentration of the luminescent substance" is for any particular purpose or to solve any stated problem that distinguishes it from the other ranges disclosed. The specification therefore lacks disclosure of the criticality required by the Courts in providing patentability to the claimed range(s).

In addition to a lack of disclosed criticality in the specification, an obviousness rejection based upon optimization must rely on prior art that discloses the optimized parameter is a result-effective variable. See MPEP 2144.05:

B. Only Result-Effective Variables Can Be Optimized

> A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be

> characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

Since Walt et al. teach that varying concentrations of luminescent substance can be used to produce luminescent silica gel particles (p4, paragraph [0046]), the prior art therefore provides teaching that the concentration of luminescent substance is a variable that achieves a recognized result, and satisfies the above requirement of a result-effective variable in order to set forth an obviousness rejection based on optimization.

Because Applicant fails to disclose that the claimed range(s) of "1 to 10%-wt concentration of the luminescent substance" provides a criticality to the invention that separates it from the other ranges in the specification, and the prior art discloses the concentration of luminescent substance is a variable that achieves a recognized result, it would therefore have been obvious for one of ordinary skill to discover the optimum workable range(s) of "1 to 10%-wt concentration of the luminescent substance" by normal optimization procedures known in the optically encoded particle arts.

With respect to claim 31, Walt et al. in view of Chen et al. teaches the spherical luminescent silica gel particles as stated above. Regarding the limitation of the luminescent silica gel particles being formed by a process comprising the steps of condensing a mixture consisting of a diluted acid and alkoxysilanes to a clear silica sol,

homogeneously mixing the clear silica sol with at least one luminescent substance to form a sol-luminescence substance mixture, dispersing the sol-luminescence substance mixture in an organic phase that is not miscible with water; and adding a base to the sol-luminescence substance mixture during or after said dispersing step in order for cross-linking said sol-luminescence substance mixture," MPEP states that the lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972). Since the spherical luminescent silica gel particles of Walt et al. reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, the spherical luminescent silica gel particles of Walt et al. anticipates the spherical luminescent silica gel particles recited in claim 31.

19. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. PG Pub. No. US 2001/0029049 A1, Oct. 11, 2001) in view of Chen et al. (*Chem. Mater.*, 1995, Vol. 7, pp1779-1783) and in light of Tjioe et al. (*Cytometry*, 2001, Vol. 44, pp24-29).

Walt et al. teaches luminescent silica gel particles (see item 15 above). Walt et al. further teaches a sensor array comprising a luminescent silica gel particles and that variety of fluorescent dyes can be employed to optically encode silica gel particles (p8, paragraphs [0081] and [0082]). However, Walt et al. fails teach luminescent silica gel particles, wherein the luminescent substance is a luminescent protein.

Chen et al. teaches a method of making optically transparent biomaterial using sol-gel encapsulation method, in which fluorescent proteins such as phycobiliproteins are added to a silica sol (see entire document, particularly p1780, *Methods*). Phycobiliproteins include phycoerythrin (PE) and allophycocyanin (APC) (p1779, *Introduction*, 2nd paragraph)

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ the sol-gel encapsulation method of Chen et al, in which fluorescent proteins such as phycobiliproteins are added to a silica sol, in order to produce optically encode silica particles of Walt et al. The advantage of optically encoding silica particles, which exhibit characteristic, i.e. unique, optical signature to a reference analyte, provides the motivation to combine teachings of Walt et al. and Chen et al. with a reasonable expectation of success as optically encoded silica particles (luminescent silica particles) with unique, optical signature can be conveniently decoded

for identification of reference analyte for use in biochemical assays. Further, it would have been obvious to one of ordinary skill in the art at the time of the invention to select a fluorescent (luminescent) protein as a fluorescent dye, since it has been held to be within the general skill of a worker in the art to select a known material on the basis of its suitability for the intended use as a matter of design choice. *In re Leshin*, 125 USPQ 416. Because the claimed particle is known in the prior art and has been disclosed as being capable of being labeled with fluorescent dyes in general, the selection of a specific type of fluorescent dyes in itself does not present a novel feature of the claimed invention. Since one of ordinary skill in the art at the time of the invention would recognize that the particle of Walt et al. could be labeled with variety of different types of fluorescent dyes known in the optical arts, it would have been obvious to employ fluorescent proteins as the fluorescent dyes in the instant claim.

Although, Walt et al. in view of Chen et al. is silent on disclosing that PE or APC has an excitation frequency higher than the emission frequency, luminescent proteins such as PE or APC of Walt et al. in view of Chen et al. intrinsically has an excitation frequency higher than the emission frequency as evidenced by Tjioe et al., which teaches that PE has excitation wavelength of 488 nm and emission wavelength of 575 nm and APC has excitation wavelength of 575 nm or 647 nm and emission wavelength of 660 nm (see entire document, particularly Fig. 1).

20. Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. PG Pub. No. US 2001/0029049 A1, Oct. 11, 2001) in view of Müeller-

Schulte (WO 02/09125 A1, Jan. 31, 2002). Official Translation of WO 02/09125 A1 has been used for the rejection below.

Walt et al. teaches luminescent silica gel particles for use in an optical chemical array sensor system (see item 15 above). Walt et al. further teaches that the particles (beads) encoded with one or more reporter dyes exhibit characteristic, i.e. unique, optical signature to a reference analyte (p4, paragraph [0050]). As a result, the individual sensor elements of the array are conveniently decoded simultaneously in one simple measurement (p4, paragraph [0050]). However, Walt et al. fails to teach luminescent silica gel particles, further comprising a magnetic colloid.

Müeller-Schulte teaches a method for producing magnetic SiO_2 particles, comprising the following steps: a) alkoxysilanes are dispersed in water, acid-catalytically hydrolyzed and condensed to form an SiO_2 hydrosol; b) a magnetic particle-sol mixture is produced by adding magnetic particles, for example usual magnetic particles, magnetic colloids and/or ferrofluids to the SiO_2 hydrosol; c) dispensing the magnetic particle-sol mixture in an organic solvent which is immiscible with water; and d) adding a base to the magnetic particle-sol mixture during or after the dispersion in the organic solvent in order to form a gel (see entire document, particularly Abstract of the WO 02/09125 A1 document). The magnetic SiO_2 particles of Müeller-Schulte can be used in variety of biochemical applications including magnetic separation assays (see p18, last paragraph-p19, first paragraph of the Official Translation of WO 02/09125 A1).

With respect to claim 16, Müeller-Schulte teaches that magnetic colloid is ferrofluids (see p6, last paragraph of the Official Translation of WO 02/09125 A1).

With respect to claim 17, Müeller-Schulte teaches that magnetic colloid is present in a concentration of 10-50% by weight relative to the polymer particle (see claim 69 of the Official Translation of WO 02/09125 A1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ the magnetic SiO_2 particles of Müeller-Schulte in the optical chemical array sensor system of Walt et al. in order to use the optically encoded luminescent silica gel particles in variety of biochemical applications including magnetic separation assays. The advantage of having both the magnetic and luminescent properties in a single particle for use in biochemical applications provides the motivation to employ the magnetic SiO_2 particles of Müeller-Schulte in the optical chemical array sensor system of Walt et al. with a reasonable expectation of success as Walt et al. teaches that variety of different types of particles can be used to produce luminescent particles.

21. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. PG Pub. No. US 2001/0029049 A1, Oct. 11, 2001) in view of Müeller-Schulte (WO 02/09125 A1, Jan. 31, 2002) as applied to claim 15 above, and further in light of Kleiber et al. (U.S. Patent No. 6,270,965, Aug. 7, 2001). Official Translation of WO 02/09125 A1 has been used for the rejection below.

Walt et al. in view of Müeller-Schulte teaches luminescent silica gel particles for use in an optical chemical array sensor system as discussed above (see item 20 above). Walt et al. further teaches that variety of functional groups such as aldehydes

(p12, Table 1 and paragraph [0108]) can be attached to the particles for adding bioactive agents. However, Walt et al. in view of Müeller-Schulte fails to teach luminescent silica gel particles, wherein the silica gels have functional groups that can be coupled to streptavidin.

Kleiber et al. teaches that aldehyde groups covalently couple with streptavidin (see entire document, particularly column 3, lines 31-36).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention would recognize that aldehyde group on the luminescent silica gel particles of Walt et al. in view of Müeller-Schulte would be capable of coupling to streptavidin.

22. Claims 19, 21-23, 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müeller-Schulte (WO 02/09125 A1, Jan. 31, 2002) in view of Chen et al. (*Chem. Mater.*, 1995, Vol. 7, pp1779-1783) and Walt et al. (U.S. PG Pub. No. US 2001/0029049 A1, Oct. 11, 2001). Official Translation of WO 02/09125 A1 has been used for the rejection below.

Müeller-Schulte teaches a method for producing magnetic SiO_2 particles, comprising the following steps: a) alkoxysilanes are dispersed in water, acid-catalytically hydrolyzed and condensed to form an SiO_2 hydrosol; b) a magnetic particle-sol mixture is produced by adding magnetic particles, for example usual magnetic particles, magnetic colloids and/or ferrofluids to the SiO_2 hydrosol; c) dispensing the magnetic particle-sol mixture in an organic solvent which is immiscible with water; and d) adding a

base to the magnetic particle-sol mixture during or after the dispersion in the organic solvent in order to form a gel (see entire document, particularly Abstract of the WO 02/09125 A1 document). The magnetic SiO_2 particles of Müeller-Schulte can be used in variety of biochemical applications include magnetic separation assays (see p18, last paragraph-p19, first paragraph of the Official Translation of WO 02/09125 A1).

With respect to claim 21, Müeller-Schulte teaches a method, wherein said organic phase contains at least one surfactive substance in a concentration of 0.1 to 15% by volume (see claims 40 and 43 of the Official Translation of WO 02/09125 A1).

With respect to claim 22, Müeller-Schulte teaches a method, wherein the volume ratio of sol to organic phase is 1:5 to 1:30 (see claim 45 of the Official Translation of WO 02/09125 A1).

With respect to claim 23, Müeller-Schulte teaches a method, wherein the said dispersing and cross-linking steps have duration of 2 to 5 seconds (see claim 9 of the Official Translation of WO 02/09125 A1).

With respect to claim 26, Müeller-Schulte teaches a method, wherein the ferro-magnetic substances added to the sol substance in an amount of 10-50% by weight. (see claim 37 of the Official Translation of WO 02/09125 A1).

With respect to claim 27, Müeller-Schulte teaches a method, further including a step of mixing an aqueous solution of organic polymer, a polysaccharide or a protein in an amount of 1-20% by volume with the sol before the dispersing step (see claims 61, 64, and 67, of the Official Translation of WO 02/09125 A1).

However, Müeller-Schulte fails to teach a method, wherein at least one luminescent substance is mixed with clear silica sol.

Chen et al. teaches a method of making optically transparent biomaterial using sol-gel encapsulation method, in which fluorescent proteins such as phycobiliproteins are added to a silica sol (see entire document, particularly p1780, Methods).

Walt et al. teaches particles (beads) encoded with one or more reporter dyes exhibit characteristic, i.e. unique, optical signature to a reference analyte (see entire document, particularly p4, paragraph [0050]). As a result, the individual sensor elements of the array are conveniently decoded simultaneously in one simple measurement (p4, paragraph [0050]).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include a step of mixing at least one luminescent substance with the clear silica sol of Müeller-Schulte as taught by Chen et al. in order to produce optically encode silica particles. The advantage of optically encoding silica particles, which exhibit characteristic, i.e. unique, optical signature to a reference analyte, provides the motivation to combine teachings of Müeller-Schulte and Chen et al. with a reasonable expectation of success as Walt et al. teaches that optically encoded silica particles (luminescent silica particles) with unique, optical signature can be conveniently decoded for identification of reference analyte for use in biochemical assays.

23. Claim 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. PG Pub. No. US 2001/0029049 A1, Oct. 11, 2001) in view of Müeller-

Schulte (WO 02/09125 A1, Jan. 31, 2002) as applied to claim 15 above, and further in view of Kleiber et al. (U.S. Patent No. 6,270,965, Aug. 7, 2001) and Tom-Moy et al. (U.S. Patent No. 5,527,711, June 18, 1996).

Walt et al. in view of Müeller-Schulte teaches luminescent silica gel particles for use in an optical chemical array sensor system as discussed above (see item 20 above). Walt et al. further teaches that variety of functional groups such as aldehydes (p12, Table 1 and paragraph [0108]) can be attached to the particles for adding bioactive agents. However, Walt et al. in view of Müeller-Schulte fails to teach luminescent silica gel particles, wherein the silica gels have functional groups that can be coupled to biomolecule streptavidin.

Kleiber et al. teaches that aldehyde groups covalently couple with streptavidin (see entire document, particularly column 3, lines 31-36). An example of a suitable immobilization method for nucleic acids include use of aldehyde groups for the subsequent covalent coupling of streptavidin or other substances which are able to immobilize binding partners by high affinity biological interactions e.g. antibodies or lectins (column 3, lines 26-41). Capture probes can be immobilized on this surface, which contain the complementary binding partner for the high affinity biological interaction e.g. biotin (column 3, lines 42-50).

Tom-Moy et al. teaches that avidin/streptavidin (column 4, lines 62-63) can be coupled to silica substrate, a biotinylated antibody can be attached to the avidin/streptavidin, and biotin can be added to block unoccupied active sites (see entire

document, particularly column 2, lines 20-37). This composite surface will bind tightly to antigen with minimal nonspecific absorption (column 2, lines 35-37).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to bind the aldehyde groups on the luminescent silica gel particles of Walt et al. in view of Müeller-Schulte with biomolecule streptavidin as taught by Kleiber et al. in order to immobilize variety of capture probes to the luminescent silica gel particles. The advantage of obtaining tight binding of an antigen of interest with minimal nonspecific absorption as taught by Tom-Moy et al. provides the motivation to bind the aldehyde groups on the luminescent silica gel particles of Walt et al. in view of Müeller-Schulte with streptavidin as taught by Kleiber et al. with a reasonable expectation of success as the luminescent silica gel particles of Walt et al. in view of Müeller-Schulte can be used to immobilize a variety of biomolecules including antibodies.

Response to Arguments

24. Rejection of claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by Walt et al.

Applicant's arguments filed on August 13, 2007 have been fully considered but they are not persuasive in view of previously stated grounds of rejection.

Applicant's arguments that Walt et al. does not teach each and every feature of the present invention as recited in claims 1-4, 6, and 25 (pp18-21) have been fully considered but are not found persuasive. Specifically, Applicant's argument that Walt et al. discloses different silica particles, which are not transparent (p19), is not found

persuasive. As stated previously, Walt et al. teaches silica particles for use in an optical chemical array sensor system (see item 13 in the previous Office Action dated April 10, 2007). According to the instant specification, silica gel particles are disclosed as being transparent (p7, paragraph [000041]). In addition, it is well known in the art that silica is transparent (see column 10, line 7 of U.S. Patent No. 5,889,798).

Applicant's argument regarding the range of silica gel particle size (pp19-20) has been fully considered, but is not found persuasive. MPEP § 2131.03 states the following:

> "[W]hen, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is anticipated' if one of them is in the prior art." *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (citing In re Petering, 301 F.2d 676, 682, 133 USPQ 275, 280 (CCPA 1962)) (emphasis in original) (Claims to titanium (Ti) alloy with 0.6-0.9% nickel (Ni) and 0.2-0.4% molybdenum (Mo) were held anticipated by a graph in a Russian article on Ti-Mo-Ni alloys because the graph contained an actual data point corresponding to a Ti alloy containing 0.25% Mo and 0.75% Ni and this composition was within the claimed range of compositions.).

Since Walt et al. teaches a range of silica particle size from about 100 nm to millimeters with preferred range of 0.5 μm to 5 μm (p9, paragraph [0089]), which covers part of the claimed range of 0.5 μm to 50 μm, Walt et al. anticipates the claimed range.

25. Rejection of claims 3-6, 14, 25, and 31 under 35 U.S.C. 103(a) as being unpatentable over Walt et al. in view of Chen et al.

As stated above in the "Rejections Withdrawn" section, the rejection of claims 3-6 and 25 under 35 U.S.C. 102(b) as being anticipated by Walt et al. has been withdrawn in favor of the new rejection of claims 3-6 and 25 under 35 U.S.C. 103(a) as set forth in

item 18 above since Walt et al. does not teach the luminescent silica gel particles, wherein the luminescent substance is luminescent protein.

Applicant's arguments with respect to claims 3-6 and 25 have been considered but are moot in view of the new ground(s) of rejection. However, Applicant's arguments with respect to Walt et al. reference have been addressed in item 24 above as they also apply to the current grounds of rejection. Further, Applicant's arguments with respect to claims 3, 5, 6, and 14 have been addressed as they also apply to the current grounds of rejection.

Applicant's argument regarding the encapsulation of luminescent compounds (claim 3) within the transparent matrix of silica gel (p20) has been fully considered, but is not found persuasive as Walt et al. does teach that various dyes can be entrapped (i.e. encapsulated) in the bead/particle matrix.

Applicant's argument regarding claim 5 (p21) has been fully considered but is not found persuasive in view of the rejection set forth in item 19 above. Applicant's argument that the claimed range of 1% to 10% luminescent substance cannot be found by pure routine experimentation as this range is preferred teaching for all particles and that routine experimentation is only possible for single species is not found persuasive. Although Applicant contends that specification (concentration of 1% to 10% luminescent substance by weight are usually adequate to achieve clear luminescence in paragraph [000057]) provides criticality of the claimed range, the cited portion of the specification merely provides working range of obtaining luminescence in the silica gel particles. However, the specification does not disclose that the specifically claimed range(s) of "1

to 10%-wt concentration of the luminescent substance" is for any particular purpose or to solve any stated problem that distinguishes it from the other ranges disclosed. The specification therefore lacks disclosure of the criticality required by the Courts in providing patentability to the claimed range(s). Since Walt et al. teach that varying concentrations of luminescent substance can be used to produce luminescent silica gel particles (p4, paragraph [0046]), the prior art therefore provides teaching that the concentration of luminescent substance is a variable that achieves a recognized result. Because Applicant fails to disclose that the claimed range(s) of "1 to 10%-wt concentration of the luminescent substance" provides a criticality to the invention that separates it from the other ranges in the specification, and the prior art discloses the concentration of luminescent substance is a variable that achieves a recognized result, it would therefore have been obvious for one of ordinary skill to discover the optimum workable range(s) of "1 to 10%-wt concentration of the luminescent substance" by normal optimization procedures known in the optically encoded particle arts.

Applicant's argument regarding claim 6 has been fully considered (p20), but is not found persuasive as Walt et al. teaches each and every feature of the present invention as recited in claims 1-4, 6, and 25.

In response to applicant's arguments against the references individually (p29), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As stated above, Walt et al. teaches luminescent silica gel particles for use

in an optical chemical array sensor system, wherein a variety of fluorescent dyes can be employed to optically encode silica gel particles (p8, paragraphs [0081] and [0082]). However, Walt et al. fails teach luminescent silica gel particles, wherein the luminescent substance is a luminescent protein. Chen et al. teaches a method of making optically transparent biomaterial using sol-gel encapsulation method, in which fluorescent proteins such as phycobiliproteins are added to a silica sol (see entire document, particularly p1780, Methods). Therefore, one of ordinary skill in the art would have been motivated to employ the sol-gel encapsulation method of Chen et al, in which fluorescent proteins such as phycobiliproteins are added to a silica sol, in order to produce optically encode silica particles of Walt et al.

26. Rejection of claim 7 under 35 U.S.C. 103(a) as being unpatentable over Walt et al. in view of Chen et al. and in light of Tjioe et al.

As stated above in the "Rejections Withdrawn" section, the rejection of claim 7 under 35 U.S.C. 102(b) as being anticipated by Walt et al. has been withdrawn in favor of the new rejection of claim 7 under 35 U.S.C. 103(a) as set forth in item 19 above since Walt et al. does not teach the luminescent silica gel particles, wherein the luminescent substance is luminescent protein.

Applicant's arguments with respect to claim 7 have been considered but are moot in view of the new ground(s) of rejection. However, Applicant's arguments with respect to Walt et al. reference have been addressed in item 24 above as they also apply to the current grounds of rejection.

27. Rejection of claims 15-17 under 35 U.S.C. 103(a) as being unpatentable over Walt et al. in view of Müeller-Schulte

Applicant's arguments filed on August 13, 2007 have been fully considered but they are not persuasive in view of previously stated grounds of rejection and response to arguments set forth in item 24 above.

28. Rejection of claim 18 under 35 U.S.C. 103(a) as being unpatentable over Walt et al. in view of Müeller-Schulte, and further in light of Kleiber et al.

Applicant's arguments filed on August 13, 2007 have been fully considered but they are not persuasive in view of previously stated grounds of rejection and response to arguments set forth in item 24 above.

29. Rejection of claims 19, 21-23, 26, and 27 under 35 U.S.C. 103(a) as being unpatentable over Müeller-Schulte in view of Chen et al. and Walt et al.

Applicant's arguments filed on August 13, 2007 have been fully considered but they are not persuasive in view of previously stated grounds of rejection and response to arguments set forth in item 24 above.

Further, Applicant's argument that none of Müeller-Schulte, Walt et al., and Chen et al. teaches the inverse suspension method of the present invention is not found persuasive as Müeller-Schulte teaches a method for producing magnetic SiO_2 particles, comprising the following steps: a) alkoxysilanes are dispersed in water, acid-catalytically hydrolyzed and condensed to form an SiO_2 hydrosol; b) a magnetic particle-sol mixture is produced by adding magnetic particles, for example usual magnetic particles, magnetic colloids and/or ferrofluids to the SiO_2 hydrosol; c) dispensing the magnetic

particle-sol mixture in an organic solvent which is immiscible with water; and d) adding a base to the magnetic particle-sol mixture during or after the dispersion in the organic solvent in order to form a gel (Abstract).

30. Rejection of claims 28 and 30 under 35 U.S.C. 103(a) as being unpatentable over Walt et al. in view of Müeller-Schulte, and further in view of Kleiber et al. and Tom-Moy et al.

As stated above in the "Rejections Withdrawn" section, the rejection of claim 28 under 35 U.S.C. 103(a) as being unpatentable over Walt et al. in view of Müeller-Schulte, and further in view of Tom-Moy et al. has been withdrawn in favor of the new rejection of claims 28 and 30 under 35 U.S.C. 103(a) as being unpatentable over Walt et al. in view of Müeller-Schulte, and further in view of Kleiber et al. and Tom-Moy et al. as Kleiber et al. teaches that the aldehyde groups of Walt et al. in view of Müeller-Schulte covalently couple with streptavidin (see the rejection set forth in item 23 above).

Applicant's arguments with respect to claim 28 have been considered but are moot in view of the new ground(s) of rejection. However, Applicant's arguments have been addressed as they also apply to the current grounds of rejection.

Applicant's arguments that Tom-Moy et al. fails to make up for the deficiencies of Walt et al. and Müeller-Schulte have been fully considered but they are not persuasive in view of previously stated grounds of rejection and response to arguments set forth in item 24 above.

31. Since the prior art fulfills all the limitations currently recited in the claims, the invention as currently recited would read upon the prior art.

Conclusion

32. No claim is allowed.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Unsu Jung whose telephone number is 571-272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Unsu Jung/
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